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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,852	11/12/2003	Gary L. Griffiths	IMMU:019US1	6078

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,852	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-18,21,23-35,38-55,57-89 and 91-125* is/are pending in the application.

4a) Of the above claim(s) *42-55,57-89 and 91-124* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9-18,21,23-35,38-40 and 125* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 10, 11-16, 21 and 38-40 have been amended. Claims 2-8, 19, 22, 36, 37, 56 and 90 have been canceled. Claims 1, 9-18, 21, 23-35, 38-55, 57-89 and 91-125 are pending. Claims 42-55, 57-89 and 91-124 remain withdrawn from consideration. Claims 1, 9-18, 21, 23-35, 38-41 and 125 are under consideration.

Applicant argues that because of deletion of reference to "nanoparticle" that the instant invention has priority to application 09/307,816, filed May 10, 1999. This has been considered but not found persuasive. The '816 application makes only one reference to an anti-CD74 antibody found in claim 33. There is no further reference in the specification, and no written description of a genus of antibodies which bind to the LL1 epitope, no description of a PEG-lipid formulated into a liposome and conjugated to a anti-CD74 antibody, no description of a composition comprising the genus of antibodies of claim 11 with the exception of anti-CD22. Further, 10/314,330 makes no mention of the LL1 antibody, and therefore does not provide an adequate written description of the instant genus of antibodies now claimed which bind to the same epitope of CD74 that is bound by the LL1 antibody. Application 09/590,284 fails to provide an adequate written description of the genus of one or more antibodies further comprised by the instant claim 11. The 10/377,122 application describes the LL1 antibody and the antibodies of claim 11, but fails to describe the PEG-lipid liposome which is conjugated to the CD74 antibody. Accordingly, the effective priority date for the instant application is commensurate with the disclosure of provisional application, 60/478,830, filed June 17, 2003.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 21, 32, 33, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for effectors which are drugs, toxins, radioisotopes or a photodynamic agent, and CD74 binding antibodies, does not reasonably

provide enablement for antibodies which bind to CD74 and effectors which are immunomodulators, is maintained for reasons of record The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 21 requires and effector which is an immunomodulator. Claim 32 is drawn to the composition of claim 1 comprising an immunomodulator. Claim 33 requires an immunomodulator which comprises various interleukins, interferons, G and GM colony stimulating factors. The art recognizes that interleukins such as Il6 and Il-10 contributed to the developments and pathogenicity of B cell lymphomas (abstract of Breen et al, Clinical Immunology, 2003, vol. 109, pp. 119-129 and the abstract of Nagel et al, Leukemia, 2005, vol. 19, pp. 841-846). The specification has not provided guidance on how to use the requires interleukins and cytokines to treat B cell lymphomas which could potentially stimulate and/or increase the malignant cells. Further regarding the teachings of Hannsen et al above, one of skill in the art would expect that the immunomodulators and interleukins conjugated to the anti-CD74 antibody would be internalized. The specification has not provided any objective evidence that an immunomodulator or interleukin delivered to the cytosol by an internalized anti-CD74 antibody would exert a therapeutic effect. Therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the instant compositions requiring immunomodulators, cytokines and interleukins.

Applicant argues that because binding to the CD74 antigen results in rapid internalization of the binding antibody, one of skill in the art would expect that the effectors, including interleukins, would be delivered to the cytosol and therefore the claim is enabled for the use of such immunomodulators. This has been considered but not found persuasive. Immunomodulators act through binding of the ligand to the cognate receptor on the cell surface causing intracellular signaling and a concomitant alteration. One of skill in the art would not expect that an immunoconjugate which delivers, Il-2 for example, to the cytosol via CD74 would trigger a signal from the Il-2 receptor on the cell surface. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to couple immunomodulators to the anti-CD74 antibody and use such conjugates for the treatment of CD74-expressing malignancies.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1, 9,10, 13-18, 20, 21, 27, 35, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al (Cancer Research, 1989, Vol. 49, pp. 4568-4577) as evidenced by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148) in view of Lundberg et al (Journal of Pharmacy and Pharmacology, 1999, Vol. 51, pp. 1099-1105) and Hansen et al (Biochemical Journal, 1996, Vol. 320, pp. 293-300) is maintained for reasons of record..

Pawlak-Byczkowska et a teach that the EPB-1 monoclonal antibody, which is identified by Juweid et al to be the LL1 antibody (Juweid, ibid, page 142, second column, last two lines). Pawlak-Byczkowska et a teach that the EPB-1 antibody discriminated between lymphoid and non-lymphoid tissue and did not cross react with solid tumor tissue specimens (abstract). Pawlak-Byczkowska et al suggest that the antibody is an appropriate candidate for radioimmunodetection and radioimmuntherapy of B cell neoplasms (page 4568, second column, lines 5-10). Pawlak-Byczkowska et al do not teach the specific composition comprising a LL1 conjugate and one or more effectors.

Lundberg et al teach conjugation of the LL2 antibody (which is the Pawlak-Byczkowska EPB-2 antibody, Lundberg, ibid, page 1099, first column, lines 8-10) with a long-circulating drug carrier lipid emulsion. Lundberg et al tech that submicron lipid emulsions have hydrophobic cores which can solubilize considerable amounts of lipophilic drugs(page 1099, second column, lines 12-14), which fulfills the specific embodiment of claim 7 requiring a nanoparticle.. Lundberg et al teach that because LL2 is internalized into cells it facilitated intracellular delivery of cytotoxic agents (page 1099, column 1-2, bridging sentence). Lundberg et al teach that the problem or rapid uptake by mononuclear phagocytes is overcome by engrafting polyethylene chains on the particle surfaces with the monoclonal antibody linked to the distal PEG terminus(page 1100, first column, lines 1-9). Lundberg et al teach the conjugation of the antibody to a lipid by a sulfide linkage to PEG (Figure 1). Lundberg et al teach the lipids of DPPc and DPPe which fulfill the embodiment of claim 13 requiring amphiphilicity. Lundberg et al teach the reaction of DSPE with the distal terminus of the PEG chain thus fulfilling the specific limitation of claim 14 requiring a nucleophilic carbon (page 1100, first column, last seven lines). Lundberg et al teach a maleimide group at a distal terminus (Figure 1, top structure) thus fulfilling the embodiments of claim 15-19. The 99-Tcm of Lundberg fulfills the specific embodiment of a diagnostic agent and a radioisotope.

Hansen et al teaches that the LL1 antibody is rapidly internalized on cells expressing the MHC I invariant chain (page 295, second column) as measured by a 111-In chelate of DTPA (page 293, second column, lines 13-14). Hansen et al suggest that the LL1 antibody is useful for the delivery of toxins, drugs or radioisotopes that can kill tumor cells expressing surface Ia, such as B cell lymphomas (page 299, last paragraph).

It would have been prima facie obvious at the tie the claimed invention was made to substitute the LL1 antibody for the LL2 antibody in the composition taught by Lundberg et al. One of skill in the art would have been motivated to do so by the teaching of Hannsen regarding the ability of LL1 to be rapidly internalized and the suggestions by both Pawlak-Byczkowska et al and Hansen et al that the LL1 antibody is useful for targeting B cell lymphomas and other B cell malignancies that express the invariant chain antigen bound by LL1.

Claims1, 9, 10, 13-18, 20, 21, 23, 27, 35, 38, and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al as applied to claims 1, 9, 10, 13-18, 20, 21, 23, 27, 35, and 125 above, and further in view of Schlom (In: Molecular Foundations of Oncology, Samuel Broader, Ed, 1991, pages 95-134)..

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph). Schlom also teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to FAb' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.

It would have been prima facie obvious at the time the claimed invention was made to provide a humanized LL1 antibody or a humanized LL1 antibody fragment, such as an scFv. One of skill in the art would have been motivated to do so by the teachings of Schlom on the necessity of avoiding the HAMA response.

Claims 1, 9, 10, 13-18, 20, 21, 23, 27, 35, 40 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al, Hansen et al and Schlom as applied to claims 1, 9, 10, 13-18, 20, 21, 23, 27, 35, and 125 above, and further in view of Greenwood et al, 'Effector functions of attached sets of recombinant human IgG subclass antibodies', In: Protein engineering of antibody molecules, for therapeutic and Prophylactic Applications in Man, Clark, Ed., 1993, pages 89 and 97).

Greenwood et al teach that for some applications it may be necessary to use an antibody isotype which is non depleting and merely targets the antigen (lines 5-6), such as IgG4, or any of theIgG2 or IgG3 which have less ability to activate complement and ADCC.

It would have been prima facie obvious at the time the claimed invention was made to use a human constant region which was IgG2a or Ig3 or Ig4. One of skill in the art would have been motivated to do so in order to have a "non-depleting" antibody which functions to bind and be rapidly internalized with and effector molecule which is a radioisotope, toxin or drug. One of skill in the art would have been motivated to o so by the teachings of Hannsen et al on the rapid internalization of the LL1 antibody and the suggestion by Greenwood et al that some applications require only a antibody targeting function.

Claims 1, 9, 10, 13-18, 20, 21, 23, 27, 35, and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al as applied to claims 1, 9, 10, 13-18, 20, 21, 27, 35, and 125 above and in further view of Nakagawa et al, (Journal of Neurooncology, 1999, vol. 45, pp. 175-183).

Claim 23 embodies the composition of claim 21 further comprising FUdR-dO Nakagawa et al teach the treatment of a patient with metastatic lymphoma to the brain with 5-fluoro-doxyuridine (Table 1, patient #16).

It would have bee prima facie obvious to one of skill in the art to use FUdR-dO within the liposomes taught by Lundberg to target non-cranial B lymphoma cells. One of skill in the art would have been motivated to do so by the suggestion by Lundberg et al that the liposomes are good carriers of drugs and the teachings of Hannsen et al on the internalization of antibodies which bind to the CD74 receptors which are present on lymphoma cells. One of skill in the art would have concluded that the killing of the cranial metastatic lymphoma cells by intrathecal administration was indicative that lymphoma cells targeted by the LL1 antibody would be similarly sensitive to the FUdR-dO.

Applicant argues that there was no reasonable expectation of success in the substitution of the LL1 antibody for the LL2 antibody. This has been considered but not found persuasive. Pawlak-Byczkowska et al suggest that the EPB-1 antibody (LL1) is an appropriate candidate for

radioimmunodetection and radioimmuntherapy of B cell neoplasms (page 4568, second column, lines 5-10). Hansen et al suggest that the LL1 antibody is useful for the delivery of toxins, drugs or radioisotopes that can kill tumor cells expressing surface Ia, such as B cell lymphomas (page 299, last paragraph). Thus, there was a reasonable expectation of success using the LL1 antibody based on the suggestion of both Pawlak-Byczkowska et al and Hansen et al.

Applicant argues that Lundberg et al is not proper prior art because it was published after the priority date. This is unpersuasive. The instant invention is entitled to the priority date of June 17, 2003, but not to the priority date of the prior filed applications for the reasons set forth above in the discussion of the priority date.

Applicant argues that the combinations of references to not provide for a PEG-lipid conjugate incorporated into a liposome. This has been considered but not found persuasive. Lundberg et al teach the same liposome resulting from stabilization of said emulsion with PEG and coupling of the antibody at the distal ends of the PEG (Figure 1 of Lundberg et al).

With regard to the remaining 103 rejections dependent on Lundberg et al, applicant argues that the supporting references fail to remedy the defects of the combination of Pawlak-Byczkowska et al (Cancer Research, 1989, Vol. 49, pp. 4568-4577) as evidenced by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148) in view of Lundberg et al (Journal of Pharmacy and Pharmacology, 1999, Vol. 51, pp. 1099-1105) and Hansen et al (Biochemical Journal, 1996, Vol. 320, pp. 293-300). this has been considered but not found persuasive because Pawlak-Byczkowska et al (Cancer Research, 1989, Vol. 49, pp. 4568-4577) as evidenced by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148) in view of Lundberg et al (Journal of Pharmacy and Pharmacology, 1999, Vol. 51, pp. 1099-1105) and Hansen et al (Biochemical Journal, 1996, Vol. 320, pp. 293-300 render obvious the instant claims 1, 9,10, 13-18, 20, 21, 27, 35, and 125 for the reasons of record set forth above.

Claims 1, 9,10, 13-18, 20, 21, 24-29, 35, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al (Cancer Research, 1989, Vol. 49, pp. 4568-4577) as evidenced by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148) in view of Lundberg et al (Journal of Pharmacy and Pharmacology, 1999, Vol. 51, pp.

1099-1105) and Hansen et al (Biochemical Journal, 1996, Vol. 320, pp. 293-300) as applied to claims 1, 9,10, 13-18, 20, 21, 27, 35, and 125 above, and further in view of Torchilin et al (Crit Rev Ther Drug Carriers, 1991, Vol. 7, pp. 275-308).

The combination of Pawlak-Byczkowska et al as evidenced by Juweid et al, Lundberg et al and Hansen et al renders obvious claims 1, 9,10, 13-18, 20, 21, 27, 35, and 125 for the reasons set forth above. The combination of references do not teach hard or soft acid chelators to chelate a radionuclide.

Torchilin et al teach the chelation of antibodies to polymers carrying the radiolabels including Bi, 99mTc and 68Ga, (page 290, line 8 and page 277, line 11 from the bottom of the page and page 303, line 6 from the bottom of the page), which fulfills the specific embodiments of claims 25-29. Torchlin et al teach the chelator of DTPA (page 278) which fulfills the specific embodiment of claims 24 and 27. Torchlin et al teach that polymers bearing the radiolabels can be chelated to targeting antibodies and result in improved radioimaging in vivo (pp. 292-303).

It would have been prima facie obvious at the time that the claimed invention was made to provide chelators and radionuclides in the immunoliposomes targeted via the LL1 antibody for the treatment of B cell neoplasm expressing CD74. One of skill in the art would have been motivated to do so because Trochlin et al teach that the chelated radionuclides can be targeted by antibodies. One of skill in the art would understand that a variety of active agents can be comprised within the immunoliposomes of Bendas, for antibody specific targeting of pathological cells.

Claims 1, 9,10, 13-18, 20, 21, 27, 34, 35, and 125are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al (Cancer Research, 1989, Vol. 49, pp. 4568-4577) as evidenced by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148) in view of Lundberg et al (Journal of Pharmacy and Pharmacology, 1999, Vol. 51, pp. 1099-1105) and Hansen et al (Biochemical Journal, 1996, Vol. 320, pp. 293-300) as applied to claims 1, 9,10, 13-18, 20, 21, 27, 35, and 125 above, and further in view of Kalluri (U.S. 7,387,779).

The combination of Pawlak-Byczkowska et al as evidenced by Juweid et al, Lundberg et al and Hansen et al renders obvious claims 1, 9,10, 13-18, 20, 21, 27, 35, and 125 for the reasons

set forth above. The combination of references do not teach the targeting of canstatin, endostatin or angiostatin as an effector.

Kalluri et al teach that Canstatin can be combined with endostatin and/or angiostatin to decrease the level of FLIP thereby triggering caspase activation and delivering a terminal apoptotic signal (column 23, line 65 to column 24, line 7).

It would have been prima facie obvious at the time that the claimed invention was made to convey canstatin, endostatin and/or angiostatin in an immunoliposome targeting B malignancies, such as the anti-CD74 immunoliposome rendered obvious by the combination of Pawlak-Byczkowska et al as evidenced by Juweid et al, Lundberg et al and Hansen et al. One of skill in the arty would have been motivated to do so in order to trigger caspase activation and subsequent apoptosis in the malignant B cell.

Claims 1, 11, 12, 20, 30, 35, 38 and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Rybak et al (U.S. 6,395,276) in view of Bendas (BioDrugs, 2001, vol. 15, pp. 215-224, IDS reference).

Rybak et al teaches an immunotoxin comprising the LL1 antibody, wherein said antibody is attached to the toxic moiety by either conjugation or recombinant means (column 12, line 47 to column 1, line 4). Rybak et al specifically teaches the LL1 immunotoxin comprising onconase (figure 3). Rybak et al teach that "Onconase" is an RNase thus fulfilling the specific requirements of an effector which is an enzyme. Rybak e al teach that immunotoxins which are directed to CD74 are useful for the treatment of B-cell malignancies wherein said B-cell has a class II invariant chain, as well as melanoma, neuroblastoma and ,myeloma (column 8, lines 64-67 and column 9, lines 55-60). Rybak et al also teach the LL2 antibody which binds to CD22 and expressed on the surface of malignant B-cells (column 9, lines 43-49). Rybak et al teach that humanized antibodies and single chain antibodies are part of the invention (column 10, lines 36-39). Rybak et al suggest possible chemical modifications of the immunotoxins of the invention include derivitization with PEG to extend half-life in the circulatory system and reduce immunogenicity as is well known in the art..

Bendas teaches two types of immunoliposomes which have the properties of prolonged systemic circulation: type I and type II, wherein type II antibodies are attached to the terminal

ends of reactive PEG derivatives (pages 216-217, bridging paragraph and Figure 2, page 218). Bendas teaches that type II immunoliposomes demonstrate increased targetability which can be attributed to the prominent positions of the antibodies t the liposomal surface (page 218, first column, lines 1-13).

It would have been prima facie obvious at the time the claimed invention was made to derivatize the LL1-immunotoxin and the LL2 immunotoxin of Rybak by making the type II immunolipsome taught by Bendas and using the immunoliposomes for the treatment of B cell malignancies. One of skill in the art would have been motivated to do so by the suggestion of Rybak et al who stated that it was well known in the art to make PEG derivatives to extent half-life in circulation and the teachings of Bendas on sterically stabilized liposomes comprising PEG which exhibit prolonged systemic circulation. Further, it would have been obvious to use both derivatized immunotoxins together for the treatment of B cell malignancies because Rybak et al teach that the anti-CD74 antibodies are useful for the treatment of malignancies.

Claims 1, 11, 12, 20, 30, 31, 35, 38 and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Rybak et al (U.S. 6,395,276) and Bendas (BioDrugs, 2001, vol. 15, pp. 215-224) as applied to claims 1, 11, 12, 20, 30, 35, 38 and 125 above, and further in view of Bagshawe et al (Curr Opin Immunol, 1999, Vol. 11, pp. 579-583)..

Claim 31 embodies the composition of claim 30 wherein the enzyme is selected from a carboxyesterase, a glucoronidase, a carboxypeptidase a beta-lacatamase, a phosphatase and mixtures thereof.

The combination of Rybak et al and Bendas render obvious the instant invention with respect to the enzyme of Onconase. Rybak et al do not specifically suggest the use other enzymatic effectors.

Bagshawe et al teaches enzymatic effectors targeted to cancer cells which include a glucoronidase, a carboxypeptidase a beta-lacatamase, and a phsophatase (page 580, Table 2).

It would have been prima facie obvious at the time the claimed invention was made to use an LL1 immunotoxin conjugated to PEG as suggested by Rybak et al, wherein the immunotoxin was a glucoronidase, a carboxypeptidase a beta-lacatamase, or a phsophatase. One

of skill in the art would have been motivated to do so by the teachings of Bagshawe et al regarding the use of said enzymes in prior antibody targeted cancer therapies..

Applicant argues that Rybak et al does not disclose the claimed composition. this has been considered but not found persuasive. Rybak et al discloses the anti-CD74 antibody binding to the LL1 epitope which is a part of the claimed composition. Rybak et al suggest that the antibody be modified by a PEG derivative to extend the half-life, and the treatment of B cell malignancies by said antibody. Bendas teaches immunoliposomes comprising PEG for extended half-life in vivo. Thus is would have been obvious to derivatize the anti-CD74 antibody of Rybak et al into the immunoliposome of Bendas because a PEG modification resulting in increased half-life is suggested by Rybak.

Claim 41 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims..

All other rejections and objections as set forth or maintained in the prior Office action are withdrawn in light of applicant's amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643